Efficacy of Retreatment After Failed Direct-acting Antiviral Therapy in Patients With HCV Genotype 1-3 Infections

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Abstract: Hepatitis C virus infection is causing chronic liver disease, cirrhosis, and hepatocellular carcinoma. By combining direct-acting antivirals (DAAs), high sustained virologic response rates (SVRs) can be achieved. Resistance-associated substitutions (RASs) are commonly observed after DAA failure, and especially nonstructural protein 5A (NS5A) RASs may impact retreatment options.1-3 Data on retreatment of DAA failure patients using first-generation DAAs are limited.4-7 Recently, a second-generation protease- and NS5A-inhibitor plus sofosbuvir (voxilaprevir/velpatasvir/sofosbuvir [VOX/VEL/SOF]) was approved for retreatment after DAA failure.8 However, this and other second-generation regimens are not available in many resource-limited countries or are not reimbursed by regular insurance, and recommendations regarding the selection of retreatment regimens using first-generation DAAs are very important. This study aimed to analyze patients who were re-treated with first-generation DAAs after failure of a DAA combination therapy.

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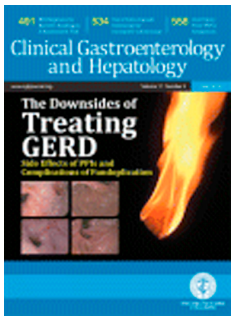

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Efficacy of Retreatment After Failed Direct-acting Antiviral Therapy in Patients With HCV Genotype 1–3 Infections

Short title: Retreatment after DAA-failure

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Abbreviations: DCV, daclatasvir; DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GT, genotype; GLE, glecaprevir; GZR, grazoprevir; ITT, intention-to-treat; LDV, ledipasvir; NS, nonstructural protein; NS3, nonstructural protein 3; NS5A, nonstructural protein 5A, NS5Ai, NS5A inhibitor, NS5B, nonstructural protein 5B, OBV, ombitasvir; PI, protease inhibitor; PIB, pibrentasvir; PTV/R, paritaprevir/ritonavir; PEG-IFN, pegylated interferon; PCR, polymerase chain reaction; RASs, resistance-associated substitutions; SMV, simeprevir, SMV; SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir; RBV, ribavirin; VOX, voxilaprevir; PrOD (Paritaprevir/Ritonavir/Ombitasvir with Dasabuvir)

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Keywords: Hepatitis C Virus, Resistance-associated substitutions, direct-acting antivirals, retreatment

INTRODUCTION

Hepatitis C virus (HCV) infection is causing chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). By combining direct acting antivirals (DAAs), high sustained virologic response rates (SVR) can be achieved. RASs are commonly observed after DAA failure and especially NS5A RASs may impact retreatment options.[1-3] Data on retreatment of DAA failure patients using first generation DAAs are limited.[4-7] Recently, a second generation protease- and NS5A-inhibitor plus sofosbuvir (voxilaprevir/velpatasvir/sofosbuvir, VOX/VEL/SOF) was approved for retreatment after DAA failure.[8] However, this and other second generation regimens are not available in many resource-limited countries or are not reimbursed by regular insurance and recommendations regarding the selection of retreatment regimens using first generation DAAs are very important. This study aimed to analyze patients who were retreated with first generation DAAs after failure to a DAA combination therapy.

PATIENTS & METHODS

Serum of patients with chronic hepatitis C was collected at different European study sites as part of a resistance database.[2] We searched the database until October 1st, 2017 for patients with a DAA failure.

Data was collected retrospectively and recommendations for retreatment were given in line with the EASL/AASLD guidelines. However, individual retreatment strategies were at the treating physician's discretion. A sustained virologic response was defined as negative HCV RNA 12 weeks after end of retreatment (SVR12). We applied a modified intention-to-treat (mITT) analysis including patients with completed retreatment and FU12. The study was conducted in accordance with the

Declaration of Helsinki and approved by the ethics committee of the University Hospital Frankfurt.

HCV NS3, NS5A and NS5B PCR and sequencing analyses were conducted as described previously.[2]

RESULTS

We investigated a cohort 631 DAA failure patients and 47% (n=262/558) of eligible patients completed retreatment (Supp. Fig. 1).

Overall 84% of NS5Ai/SOF failures infected with GT1 achieved SVR. The majority of patients received a regimen including a PI plus SOF (SMV/SOF±RBV, SMV/SOF+DCV/LDV, PrOD/SOF±RBV, GZR/EBR+SOF) and the SVR rate was 91%. All patients without NS5A RASs achieved SVR, while the SVR rate was 90% in presence of RASs and Y93 RASs reduced SVR rates. A PI-based regimen without SOF (PrOD±RBV, GZR/EBR) was less effective (82% SVR) with slightly lower SVR rates in GT1a compared to 1b. For PI-based regimens in absence of RASs, the SVR rate was 93% and NS5A RASs reduced SVR rates. A repetition of NS5Ai/SOF without a PI was ineffective with 68% SVR. Here, in absence of RAS, the SVR rate reached 88% and was 50% only in presence of RAS (Fig. 1A-D).

All GT3 DCV/SOF failures were retreated NS5Ai/SOF-based and 60% achieved SVR. The majority of patients harbored NS5A RASs (93%), and SVR rates were higher in absence of cirrhosis or absence of Y93H (Fig. 1E/F). We detected no statistically significant differences between SVR and failure patients concerning the presence of cirrhosis and other clinical parameters (Supp. Table 1). Data regarding treatment adherence, liver fibrosis and portal hypertension was not available as

patients with decompensated cirrhosis were not included and therapies were conducted at external centers.

DISCUSSION

The management of DAA failure patients remains a challenge. Our study comprises a very large European real-world DAA failure cohort and 85% achieved SVR upon retreatment with first generation DAAs.

We demonstrated high SVR rates after NS5Ai/SOF failure in GT1, when SOF was reused in combination with a new DAA class (i.e. switch from a NS5Ai to a PI). However, SVR rates were slightly reduced in presence of high-level resistant Y93 RASs. A retreatment based on the addition of a new DAA class without SOF as well as repetition of NS5Ai/SOF led to reduced SVR rates in presence of NS5A RASs and especially GT1a patients with high-level resistant Q30R responded poorly. These strategies may be considered in the absence of NS5A RASs only.[6]

In DCV/SOF failures with GT3, the prevalence of NS5A RASs as well as cirrhosis was considerably higher compared to GT1. SVR rates to a NS5Ai/SOF repetition, were low especially in presence of cirrhosis or Y93H. Interestingly, in a recent study with inclusion of a PI (VOX/VEL/SOF) the majority of treatment failures had GT3.[8] Thus, retreatment of GT3 remains a challenge.

Limitations of this study include the retrospective data analysis and small patient numbers in specific groups. Taken together, for GT1-infected patients including a new DAA class plus sofosbuvir is highly effective, whereas retreatment of GT3 is requiring multiple targeted regimens including a second generation PI. The results of this real-world study may be of importance for many areas of the world where second generation therapies are not available or not affordable.

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FIGURE LEGENDS:

Fig. 1: Retreatment in patients with NS5Ai/SOF failure. SVR rates according to (A) retreatment regimens (GT1); RASs in (B) patients who received a new DAA class plus SOF (GT1); (C) individuals who were retreated with new DAA class without SOF (GT1); (D) patients who received a repetition of NS5Ai/SOF (GT1); (E) retreatment regimens (GT3); RASs in (F) DCV/SOF failures (GT3).

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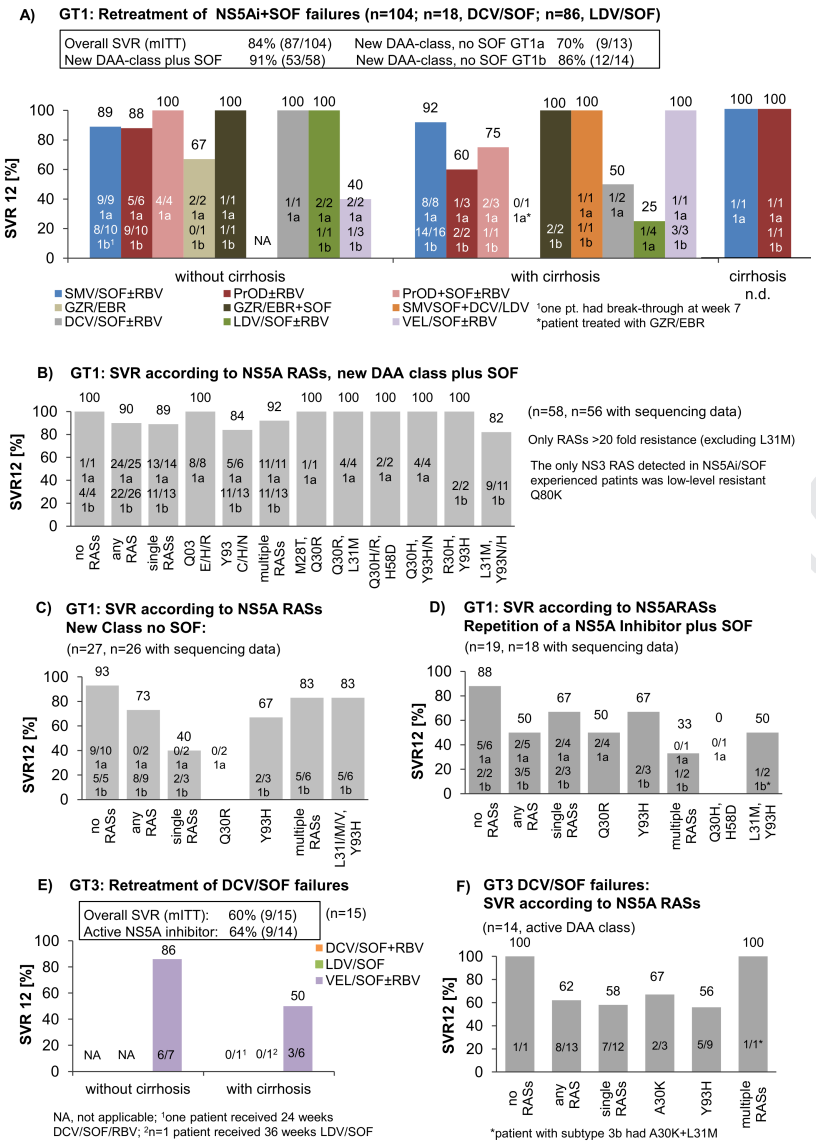
338 (Bielefeld); E. Zehnter (Dortmund); A. Zipf (Mannheim).

Figure 1

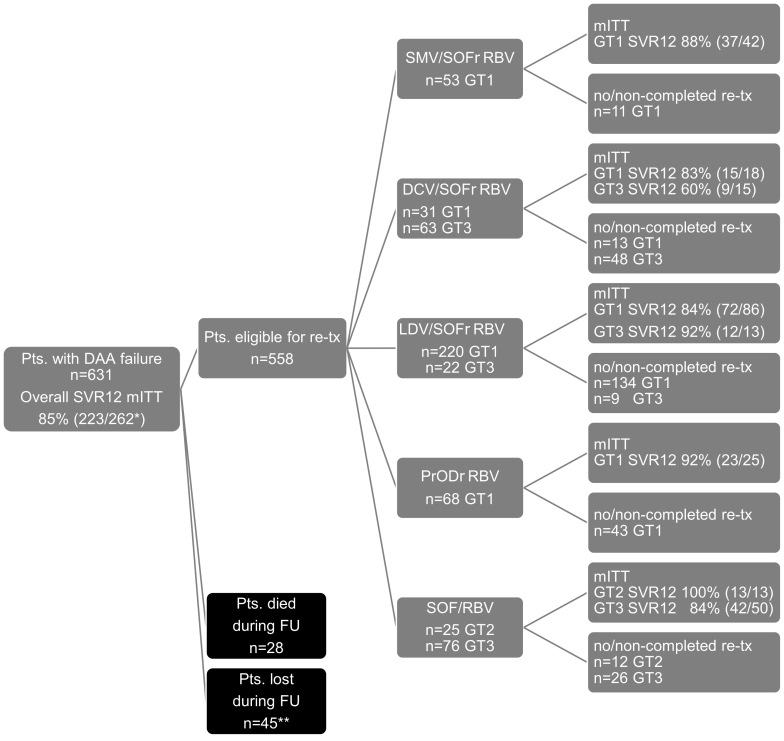


Supporting Table 1. Characteristics of patients eligible for retreatment infected with HCV genotype 1 (n=251) and genotype 3 (n=63).

	DCV/SOF±RBV, HCV GT1, n=31			LDV/SOF±RBV, HCV GT1, n=220			DCV/SOF, HCV GT3, n=63		
	Re-Tx n=18 (58%)		No Re-Tx[§] n=13 (42%)	Re-Tx n=86 (39%)		No Re-Tx[§] n=134 (61%)	Re-Tx n=15 (24%)		No Re-Tx[§] n=48 (76%)
	SVR n=15 (83%)	FAIL n=3 (17%)		SVR n=72 (84%)	FAIL n=14 (16%)		SVR n=9 (60%)	FAIL n=6 (40%)	
GT1, subtype 1a	7 (47)	2 (67)	9 (69)	36 (50)	7 (50)	69 (52)	-	-	-
GT1, subtype 1b	8 (53)	1 (33)	4 (31)	36 (50)	7 (50)	63 (47)	-	-	-
GT1, subtype other	-	-	-	-	-	2 (1)	-	-	-
GT3, subtype 3a	-	-	-	-	-	-	8 (89)	6 (100)	40 (83)
GT3, subtype 3b	-	-	-	-	-	-	1 (11)	-	1 (2)
GT3, subtype 3h	-	-	-	-	-	-	-	-	1 (2)
GT3, subtype other	-	-	-	-	-	-	-	-	6 (13)
Male gender	13 (87)	2 (67)	8 (62)	56 (78)	12 (86)	98 (73)	8 (89)	6 (100)	41 (85)
Mean Age	53 (33-63)	58 (54-61)	54 (28-71)	59 (36-77)	57 (30-74)	57 (24-84)	51 (37-60)	54 (45-54)	50 (31-65)
Cirrhosis	10 (71) n=14*	2 (67) n=3*	5 (46) n=11*	28 (40) n=70*	8 (57) n=14*	50 (39) n=129*	3 (33) n=9*	5 (83) n=6*	15 (33) n=45*
Prior IFN-experience	9 (69) n=13*	1 (33)	7 (78) n=9*	38 (59) n=64*	6 (55) n=11*	39 (39) n=100*	4 (80) n=5*	5 (100) n=5*	18 (56) n=32*
RBV included in 1st treatment	3 (20)	2 (66)	3 (23)	20 (28)	4 (29)	30 (22)	0 (0)	2 (33)	6 (13)
Duration 1st DAA treatment	n=15*	n=3*	n=11*	n=63*	n=13*	n=107*	n=9*	n=6*	n=40*
8 weeks	-	-	-	20 (32)	3 (23)	37 (35)	-	-	-
12 weeks	7 (47)	2 (67)	7 (64)	36 (57)	10 (77)	61 (57)	7 (78)	4 (67)	28 (70)
24 weeks	8 (53)	1 (33)	3 (27)	7 (11)	-	8 (7)	2 (22)	2 (33)	12 (30)
Early discont.	-	-	1 (9)	-	-	1 (1)	-	-	-
Retreatment									
RBV included in Retreatment	13 (87)	1 (33)	n.a.	38 (53)	9 (64)	n.a.	5 (71)	5 (83)	n.a.
Duration Retreatment									
12 weeks	7 (47)	2 (67)		52 (72)	8 (57)		6 (67)	4 (67)	
24 weeks	8 (53)	1 (33)		19 (26)	5 (38)		3 (33)	2 (33)[+]	
Early discont.	-	-		-	1 (5)		-	-	
Resistance after DAA failure									
Pts. with NS3 RASs[#]	1 (7) n=14	2 (67) n=3*	5 (46) n=11*	14 (20) n=70*	1 (8) n=13*	32 (24) n=133*	- n=5*	- n=5*	- n=18*
Pts. with NS5A RASs[#]	12 (86) n=14*	3 (100) n=3*	5 (46) n=9*	55 (79) n=70*	11 (85) n=13*	107 (84) n=127*	8 (89)	6 (100)	36 (82) n=44*
Pts. with NS3any + NS5Aany	2	1	1	5	-	24	-	-	-
NS3 Q80K	2	1	3	13	-	26	-	-	-
NS3 R155K, A156any, D168any	-	-	2	1	-	6	-	-	-
NS5B S282T	-	-	-	-	-	2	-	-	1

DAA, direct acting antiviral; DCV, daclatasvir; FAIL, failure; IFN, interferon; LDV, ledipasvir; n.a., not applicable; NS3, nonstructural protein 3; NS5A, nonstructural protein 5A; SOF, sofosbuvir; pts., patients; RBV, ribavirin; Re-Tx, retreatment. *Number of patients with available data; [#]Rate of pts. with RASs; [+]One pt. received 36 weeks LDV/SOF; [§]status of October 2017 (see methods).

Supplementary Figure 1



mITT (modified ITT): Retreatment with completed FU
no/non-completed re-tx: with status of October 2017 (see methods).
re-tx: retreatment
*patients with FU12 data available
**includes n=6 pts. with development of HCC